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Reprinted from:
Neural and Behavioral Specificity
STUDIES ON THE DEVELOPMENT OF BEHAVIOR
AND THE NERVOUS SYSTEM, VOL. 3
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ACADEMIC PRESS, INC.
New York San Francisco London

RETINOTECTAL SPECIFICITY: CHEMOAFFINITY THEORY

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I. Introduction

The early studies on retinotectal regeneration showed with behavioral tests that the functional properties mediating visual direction and involving the "local sign," or "positional" specificity in the retinal field are restored in accurate detail in regrowth of the optic nerve onto the midbrain tectum and that this orderly recovery occurs regardless of maladaptive behavioral effects (Sperry, 1943, 1944, 1945). By combining behavioral tests with selective tectal lesions, it was shown further that the orderly restitution of behavioral properties reflects an underlying order in the anatomical remapping

of fiber projections on the tectum. Anterior, dorsal, or posterior tectal ablations before and after optic nerve regeneration in five species from three genera of adult anurans confirmed a topographic plan in retinotectal projection in the normal state and also demonstrated its selective reestablishment in regeneration (Sperry, 1944). The tectal lesions after optic nerve regeneration produced differential blind areas or scotomata comparable in location and in size to those produced prior to optic nerve section.

From these and related findings (Sperry, 1951a) it was concluded that ganglion cells of each retinal locus are normally destined to grow connections with a corresponding complementary locus in the tectum. It was inferred that retinal and tectal neurons must acquire through developmental differentiation cell-unique specific cytochemical properties that serve to identify each cell and its optic fiber extensions in accordance with the position occupied by the cell body within the retinal or tectal field. For each locus in the retina there must exist a corresponding complementary or matching locus in the tectum for which the retinal fibers have preferential chemical affinity. Midbrain transection and regeneration of the tectospinal tracts combined with eye rotation in *Triturus* (Sperry, 1948) gave further evidence for the differentiation of locus specificity among the tectal neurons.

The required distribution of retinotectal specificities and affinities was thought to be achieved through a polarized, fieldlike, or gradient type of morphogenetic differentiation, first along the anteroposterior (i.e., rostrocaudal or nasotemporal) axis and then later on the dorsoventral axis of the developing retinal and tectal fields, these being conceived as subfields within the main axial gradients of the embryo (Sperry, 1944, 1965a). This means each neuron has its latitude and longitude, so to speak, encoded in its chemistry. Positional specificities in the tectum have certain properties complementary to those in the retina. Selective patterning of fiber aggregations and trajectories along the course of the optic nerve tracts and tectal radiations also were attributed to chemotactic guidance regulated by the same kinds of preferential cytochemical affinities (Attardi & Sperry, 1963; Sperry, 1963).

In addition to the locus specificities associated with retinal and tectal gradients and with directionality in visual space, it was possible to infer from behavioral tests after optic nerve regeneration the presence also of other dimensions of cell specificity, like those for mediation of learned color discrimination, luminosity, on–off, and off–on effects (Arora & Sperry, 1963; Sperry, 1965a). Each individual optic axon and even each microfilament of its growth tip was inferred to contain typically several modes of molecular specificity that help regulate chemotactic guidance to proper synaptic zones and selective reinnervation of correct target cells within the terminal synaptic zone.

It was not a precise cell-to-cell connectivity that was inferred, but rather cell-to-focal tectal area with extensive terminal overlap among neighboring fibers (Sperry, 1951b, 1958). The competitive interaction among overlapping terminal arbors for synaptic sites and appropriate density of innervation was conceived to involve preferential, graded affinities, not all-or-none selectivity. Various other trophic, denervation, saturation, and related general factors were presumed to be operative (Sperry, 1951a). The preferential chemoaffinity effects were described as based on embryonic gradient and morphogenetic field systems, and other mechanisms of cell differentiation. Failure to include these developmental concepts and properties in the interpretation of neurospecificity theory has been a continuing source of confusion. These concepts do not exclude plasticity of developmental, experiential, or other sorts. Ideas that the resultant connectivity is necessarily rigid, prefixed, or exclusive have arisen mainly in reference to subsequent findings.

The appearance of this interpretation in the early 1940s directly reversed the prevailing doctrine of the time in which nerve growth was held to be diffuse and nonselective, with chemical and electrical theories ruled out in favor of mechanical guidance. It introduced a new order of complexity and refinement to concepts of cell differentiation and intercellular affinity in general that extended to the level of individual cells, paralleling functional differentiation throughout the sensorineuromotor system. Early objections that there were not enough distinct molecular species available subsided with advances in molecular biology.

Mainly the interpretation gave us a much needed explanatory scheme for the inheritance and prefunctional organization of the neural circuits for innate behavior, replacing concepts like "neurobiotaxis," "disuse atrophy," "equipotential nerve nets," and "resonance," and providing a credible neurogenetic basis for ethology. On these terms, function was conceived to play an important role in shaping innate behavioral traits, not during development, but indirectly over the span of generations acting as a selection factor for differential preservation of genetic variations. These genetic factors control in turn neuronal specification, which determines fiber connection patterns. The scheme allows plenty of leeway for the added effects of learning and other forms of neural plasticity, including functional modulation and fine tuning of genetically determined neural structure during growth and development. The alternative suggestion that the fundamental neural connectivity is wired up on the basis of impulse specificity in different neurons (Chung, Gaze, & Stirling, 1973; Keating, this volume) seems contraindicated by the evidence, as does the earlier proposal by Weiss (1931) along similar lines (Sperry, 1965b).

This general explanatory model has since been reinforced and refined by

numerous electrophysiological, anatomical, and behavioral studies and has been found to apply equally well to other neuronal systems, such as the vestibular, cutaneous, oculomotor, and tectospinal pathways (Gaze, 1970; Jacobson, 1970; Sperry, 1951a, 1965a), and also to invertebrates (Baylor & Nicholls, 1971; Edwards & Palka, 1971). Further, a direct histological demonstration of the chemoaffinity hypothesis was obtained by combining nerve regeneration with retinal lesions in goldfish (Attardi & Sperry, 1963). This and similar subsequent experiments on both goldfish (Jacobson & Gaze, 1965; Roth, 1972; Westerman, 1965) and chick (Crossland, Cowan, Rogers, & Kelly, 1974; De Long & Coulombre, 1965) appear to confirm that the growing optic fibers show a selective preference for their correct tectal regions despite opportunities to terminate incorrectly in neighboring denervated areas.

Meanwhile, more recent studies have been interpreted as showing results inconsistent with the original hypothesis (Gaze, 1970). Compound eyes formed in frog embryos from two nasal or two temporal half-retinas were found to form their synaptic connections across the entire tectum (Gaze, Jacobson, & Székely, 1963, 1965). Also, in goldfish it was found that a remaining anterior half-tectum, after ablation of the posterior tectum, accepted orderly connections from the entire retina (Gaze & Sharma, 1970). In order for the whole retina to remap on the half-tectum, it appeared that the original synaptic connections in the intact half must break down and reform more anteriorly, while the optic fibers formerly connected to the excised tectum must form synapses with entirely new cells to which they normally never connect. To account for these and related findings, as described by Keating in the preceding article in this section, Gaze (1970) proposed a modified sliding scale or "systems matching" hypothesis whereby optic fibers form their terminals not at predestined targets but at correct relative positions along whatever fraction of tectal gradient is available. Later work by Yoon (1971, 1972a) and Sharma (1972a, 1972b) seemed to confirm the lack of predetermined connectivity. Yoon in particular reported further that the process of compression of the retinal projection map onto a half-tectum was reversible under conditions where the tectum was divided with a barrier of Gelfilm, which later resorbed. Other types of compound eyes, like nasal-ventral (Hunt & Jacobson, 1973a) or double-ventral eyes (Straznicky, Gaze, & Keating, 1974), have produced complex tectal projections that cannot be easily understood as the simple sum of the original retinal halves.

The interpretation is additionally complicated by apparent inconsistencies in the goldfish work and by lack of agreement between the electrophysiological data on which the evidence for plasticity has rested and

correlated anatomical data. Yoon (1972b) and Horder (1971) both reported electrical evidence for uniform spreading of a surgically formed half-retina over an entire normal tectum. In contradiction, the original study of Attardi and Sperry (1963), using Bodian staining, and Roth's (1972) recent similar work showed that these same half-retinas preferentially terminated in the appropriate tectal region. Yoon (1972b) and Horder (1971) had further electrophysiological data apparently showing that if noncomplementary retinal and tectal halves were removed, the remaining retina spreads over the entire inappropriate half-tectum. Under these same conditions the anatomical evidence of Roth (1972) indicated that innervation was restricted to the region near the lesion, leading much of the tectum without optic fibers.

Further, the electrophysiological evidence has seemed in part self-contradictory. While Yoon (1972b) reported that both nasal and temporal hemiretinas showed plasticity, Horder (1971) had evidence that only a nasal half-retina expanded in this manner; and Jacobson and Gaze (1965) had data suggesting neither half did this. Although only a rough mediolateral incision was sufficient to induce complete field compression onto the rostral tectum in Yoon's hands (1971), a similarly placed even larger lesion did not produce this result in Sharma's (1972b) experiment. Medial or lateral tectal ablations had been reported not to result in plastic remapping (Jacobson & Gaze, 1965), and the suggestion that this could be a consequence of interference with the medial optic tract was later supported in the results of Yoon (1971). Yet, according to Sharma (1972b), removal of the rostral tectum, causing comparable tract damage, did cause compression of visual field representation onto the caudal tectum. In the study of Gaze and Sharma (1970), simple removal of the caudal tectum regularly resulted in their finding rostral tectal loci from which two widely separated receptive fields could be recorded. Not one instance of this field duplication was found by Yoon (1971).

In neonatal rodents various alterations in retinal projection following different collicular and retinal lesions (Lund & Lund, 1973; Schneider & Jhaveri, 1974) raise questions about the role of chemoaffinity in the development of this system. In neonatal rats a mediolateral inversion of the retinal projection to ipsilateral colliculus formed after unilateral eye removal has been interpreted as contradicting chemoaffinity (Cunningham & Speas, 1975).

In the face of these mounting disparities and contradictions in the literature, it becomes increasingly difficult to see any uniform interpretation for the formation of retinotectal connections. The following is directed at some of the main discrepancies in the evidence and interpretations and includes new results of relevant recent experiments by the first author.

II. Compound-Eye Experiments

The projection maps obtained from experimentally formed compound eyes first raised serious questions about the chemoaffinity model. Compound eyes were formed surgically in amphibian embryos by removing the nasal or temporal half of the eye anlage and replacing it with a mirror half-eye from a donor. These double-nasal or double-temporal compound eyes eventually formed, in most cases, eyes of normal size and general appearance and developed functional retinotectal connections. The initial experiments were carried out by Székely (1954) in *Triturus*. He found visually guided behavior from such eyes to be abnormal. Although all animals reacted to stimuli over the entire field, the double-nasal animals acted as if the objects they saw were only in the temporal field, and the double-temporal animals localized all visual stimuli into the nasal field. Further, when the caudal half of the tectum was ablated, the double-nasal animals became blind, whereas the double-temporal animals were blinded by rostral tectal lesions. All these results were entirely in accord with the original chemoaffinity predictions.

Subsequent compound eye studies, however, by Gaze *et al.* (1963, 1965) using *Xenopus* and electrophysiological mapping methods gave different results. Each half of the compound eye was found to project topographically and in overlapping manner across the entire tectum with the nasotemporal orientation for each hemiretina reversed (Fig. 1). It was further shown by Straznicky, Gaze, and Keating (1971) that after metamorphosis,

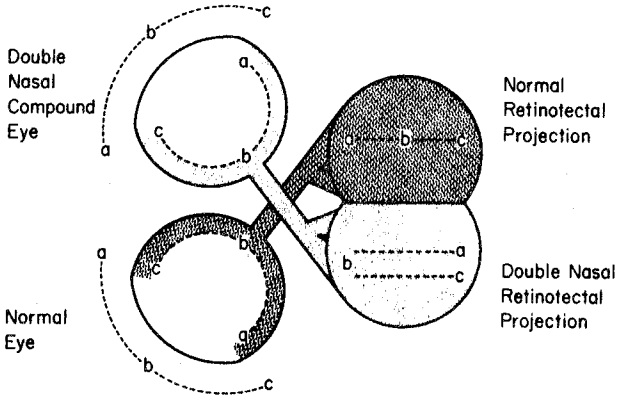

FIG. 1. Diagram of the visual field and retinotectal projection in an adult *Xenopus* with a double-nasal compound eye formed embryonically by surgically removing the temporal half of the eye vesicle and substituting from a donor a nasal half-vesicle mirror image to the nasal half left in the orbit.

when tectal development is largely completed, the fibers from the compound eye, after being sectioned and uncrossed at the chiasm, would regenerate ipsilaterally to again form a similar projection onto the ipsilateral tectum which had been normally innervated throughout development. This ruled out an interpretation suggested earlier (Sperry, 1965a) in terms of selective developmental hyperplasia of the appropriate innervated half-tectum, with hypoplasia of the uninnervated half, as had been obtained with surgically produced variations in eye size (Harrison, 1929; Stone, 1930).

The observed projection in *Xenopus* of each compound half-retina across the entire tectum in reverse orientation seemed to require a modified hypothesis in which it was proposed that the optic fibers, instead of finding predesignated tectal sites, arrange themselves during growth in an orderly way as a competing system that fills up whatever gradient is available. This view retains the concept of cytochemical specificities arranged in gradient fashion, but the nerve connections are established on a flexible or sliding scale instead of one that is prefixed. This sliding scale or "football field" interpretation (Gaze, 1970) seemed to gain further reinforcement in later experiments demonstrating compression and expansion in the retinotectal system. This modified interpretation is incompatible with some of the early retinotectal data, as will be discussed more fully later, and particularly with recent findings on half-tectum frogs.

We have long favored a quite different explanation of the compound eye experiments (Meyer & Sperry, 1973, 1974; Sperry, 1965a) as follows: It is known that a morphogenetic field almost by definition (Weiss, 1939), if cut in half during early development, can be expected to undergo self-regulation to reorganize itself into a whole field. Such a reorganization of each half-retina would account for spread of the projection from each hemiretina over the entire tectum. We need merely suppose that each half-retina, when confronted with the reverse gradient forces of the other half, responds by forming a whole retinal field of its own, reduced in size and modified somewhat in shape to fit the existing confinements.

Thus, the compound eye in the *Xenopus* experiments may be thought of as having developed two full twin retinal fields, so far as the rostrocaudal gradient is concerned. These twin retinas are reduced in size and are set as mirror images joined near the vertical midline of the eye, with the rostrocaudal gradient of each twin reversed so that there is no abrupt break in cytochemistry in passing from one twin to the other. The resultant projection pattern on the tectum would be of the form obtained by Gaze *et al.* (1963, 1965). This kind of plastic reorganization of locus specificities involving morphogenetic regulation was always implicit in the chemoaffinity interpretation as evidenced in the prediction that the dorsoventral gradient might be reversed independently of the anteroposterior (Sperry, 1944) if the surgery

were properly timed. The variables in the compound eye results, thus conceived, would no longer be a matter of the way in which nerve fibers grow and connect, but a question, rather, of the precursor developmental dynamics by which neurons acquire specificity. If the surgery is performed at a stage after the gradient properties and positional specificities have already become irreversibly fixed, the predicted tectal projection on these terms will be of the form obtained by Székely (1954), whereas there is no accounting for such results in the "sliding scale" hypothesis. The double-retina interpretation finds indirect support in the observation that a double lens is sometimes formed in the compound eye (Gaze, Keating, Székely, & Beazley, 1970). Also, it is known from the early work of Harrison (1921) that when the embryonic field of the developing limb bud is treated by analogous surgical procedures, the compound limb bud will frequently form two separate duplicate limbs oriented in mirror-image fashion, like the twin retinas.

The kind of retinal reorganization inferred for the compound eye does not involve a reversal of gradient polarity in either hemiretina, but only readjustments of scale in the preexisting gradients. There is an important difference between changing the direction of a gradient and merely altering its extent or range (Meyer & Sperry, 1973). The compound eye surgery was performed at a stage in which the retinal gradients are now known to be no longer plastic to reversal by eye rotation (Jacobson, 1968a), but this does not preclude the kind of plasticity involved in reorganizing a half-scale gradient into a whole-scale gradient.

The presence of regulative plasticity of the kind required is indicated in an early behavioral study of Székely (1957) on *Triturus*. He removed the nasal or temporal half of presumably "specified" eyes and rounded up the intact half into a small eye, which eventually developed into an eye of about half-normal size. Visual testing revealed only normal responses over the entire visual field with no indication of the directional distortions that would be expected had the halved retina not undergone reorganization into a whole-scale field. This same result was later confirmed by Gaze (1970) in *Xenopus* with electrical mapping, which showed a predominantly normal retinal projection across the entire tectum. Both results are most simply explained on the assumption that the remaining half-retina developed into a whole retina.

Further evidence for plasticity in these early retinal fields has been found recently by Hunt and Jacobson (1973a). Compound eyes in *Xenopus* made of nasal and ventral or nasal and contralateral temporal half-retinas were found to form projections in which each half-retina spread connections across the entire tectum. Even simple surgical bisection of the eye anlage resulted in mirror twinning of retinal projection (Hunt & Jacobson, 1973b). Sharma and Hollyfield (1974) obtained a similar compound type projection in one case in *Rana pipiens* simply by eye rotation. Both these findings are

reminiscent of previous limb bud experiments showing mirror duplication after surgical splitting or rotation of a developing limb field (Harrison, 1921) and add to the growing support for the "mirror twinning" interpretation. Embryonic retinal regulation is also strongly indicated by the axial reversals found in the compound eyes of Hunt and Jacobson (1973a), by the distortions found to occur in the tectal projection from double ventral compound eyes (Straznicky *et al.*, 1974), and by a variety of alterations recently found in other types of compound eyes (Hunt, 1975).

In other respects also the compound eye findings lend further support to chemoaffinity principles by furnishing new evidence against any simple mechanical or temporal scheduling in favor of guidance by prescribed affinities as follows: Compound eyes have been shown to grow in the same manner as normal eyes, largely by slow annular addition of cells at the margin (Feldman & Gaze, 1972). Central retinal cells differentiate and send out axons well in advance of the peripheral retinal cells. In contrast to normals, where central retinal cells project to the central tectum, the central cells in compound eyes project to the tectal margin, the rostral margin in the case of double-nasal eyes, and the caudal margin in the case of double-temporal eyes. This differential but orderly projection, under abnormal mismatch conditions, which occurs in spite of apparently identical timing and positional factors, is difficult to account for by other than some orderly intrinsic specificities in the ganglion cells with preferential affinities for particular central pathways and tectal terminations.

III. Determination of Positional Specificity

The prediction that specification of retinal ganglion cells involves differentiation on at least two separate axial gradients and occurs first on the anteroposterior (rostrocaudal or nasotemporal) axis and later on the dorsoventral axis, and that this could be demonstrated by surgical inversion of the eye at successively earlier stages (Sperry, 1944) was confirmed by Stone (1944), by Székely (1957), and by others since. Prior to a certain stage of development one expects surgical eye rotation to be readjusted by plastic embryonic processes that restore the conditions for normal retinotectal projection. As growth proceeds, the developmental capacities for such corrective readjustment are lost, and thereafter surgical rotation and other rearrangements produce corresponding distortions in retinotectal mapping and visual behavior (Fig. 2). During the critical period in which this change-over occurs, the cytochemical gradient properties of the intact eye become irreversibly determined and regardless of surgical rotation or heterotopic transplantation, they express thereafter their original chemoaffinities.

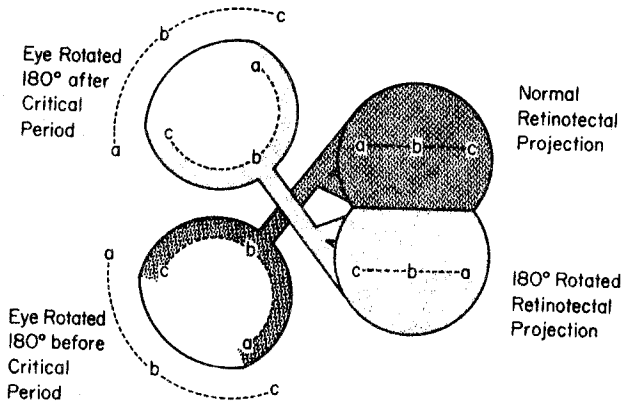

FIG. 2. Diagram of the visual field and retinotectal projections of an adult amphibian after prior 180° rotation of the eye vesicle in the embryo before or after the critical period.

Experiments have been undertaken in and around the changeover period in an effort to find clues as to the nature of the specification process at the cellular and molecular level. Thus on the basis of thymidine labeling studies for DNA synthesis, Jacobson (1968b) suggested that neuronal specification occurs only after cessation of DNA synthesis, which was found to coincide with the end of the critical period. Prior to that (Stage 29 for *Xenopus*), the retinal ganglion cells were conceived to be "unspecified . . . did not know what their central connections should be, and received their information only after Stage 29" (Jacobson, 1970). In the original chemoaffinity interpretation the specification process was conceived somewhat differently. The eye, limb, and other organ fields were described as emerging in treelike fashion as subfields out of the main axial gradients of the embryo (Sperry, 1965a), in accordance with standard developmental doctrine. The specification process itself thus starts much earlier in this view and is traceable back to the initial polarization of the embryo as a whole. The finding that surgical inversion yields normal visual projection prior to Stage 29 and inverted vision afterward is taken to mean only that the specification process is no longer reversible after Stage 29. In these terms, the so-called critical period as revealed by grafting procedures is not when specification occurs, but only when the process reaches the stage of irreversibility (Meyer & Sperry, 1973).

The chemical differentiation underlying the specification process is conceived to start in simple form and to become increasingly complex and defined by stages involving multicellular interactions. Different phases and features of this complex biochemical process become fixed and irreversible

at different times. For example, the positional specificities in a gradient may be irreversibly determined so far as reversal by eye rotation is concerned, but still remain plastic in regard to compression or expansion of the same gradient with its polarity unchanged (Meyer & Sperry, 1973). The critical stage for polarity reversal may be different also for different conditions, such as 180° rotation of the eye, inversion on one or the other axis only, or inversion of only one-half of a compound eye. From general developmental considerations intraretinal interactions can be expected to be of developmental consequence even after eye–body interactions have largely ceased. Such experiments tell us little about either the initiation or the completion of the specification process, only about its maturational stages and progressive loss of flexibility. On these terms the cessation of DNA synthesis in *Xenopus* might be a useful clue to the nature of the post-critical-period irreversibility, not necessarily the end product of specification. Possible significance of the observed correlation with DNA synthesis is dimmed by a recent failure to find it in *Rana pipiens* (Sharma & Hollyfield, 1974) and evidence that even in *Xenopus* most ganglion cells are formed after the critical period (Straznicky & Gaze, 1971).

The foregoing view of the specification process receives further experimental support from an important series of recent eye transplant experiments by Hunt and Jacobson (1973c). The eye vesicle in *Xenopus* embryos was removed at Stages 22–24, well before the critical period of Stages 28–32, and either transplanted to a neutral belly midline position in a carrier embryo or to cultures *in vitro* in which the eye developed to Stage 39/40. Subsequent reimplantation into the enucleated orbit of a Stage 39/40 host produced a retinotectal projection corresponding to the eye's original normal polarity, indicating that the developing eye even before the critical period possesses axial information and that the process of polarization can proceed *in vitro* independently of the embryo. In another series of inter-embryo transplants, systematic variation of the stages of both donor and host embryos showed that the final irreversible fixation of polarity was dependent primarily upon intrinsic factors within the eye (Hunt & Jacobson, 1974). Based on these and related results, Hunt and Jacobson (1973b, 1973c, 1974) have redefined their original use of "specification" (Hunt & Jacobson, 1972a, 1972b) to mean the irreversible fixation of axial polarity.

The precise timing and molecular mechanisms underlying the sequence of events in specification that ultimately lead to acquisition of cytochemical properties regulating selective fiber outgrowth and synapsis remain to be elucidated and presumably are closely tied to the basic mechanisms of cell differentiation. The recent demonstration that in *Xenopus* tadpoles there is a progressive caudal shift of the retinotopic projection across the growing tectum (Gaze, Keating, & Chung, 1974) does not contradict the idea of

preferential terminations since it may only reflect developmental changes in the cytochemical properties of the enlarging retina or tectum. Even if one assumes a stable and final cytochemical differentiation, the presumably inappropriate retinal projection onto rostral tectum at early tadpole stages may be explained along lines similar to that proposed for plastic remapping of the retina into a surgically formed rostral half-tectum in goldfish (see Section IV on tectal lesions).

Caution is warranted, however, by recent questions about the nature, reality, and generality of the plasticity (Hunt & Jacobson, 1973b). It is not found apparently in chick embryos (Crossland *et al.*, 1974; De Long & Coulombre, 1965) even though, like tadpoles, fiber ingrowth is at the rostral end of the tectum. In chicks there is also evidence for an early specification of retina. Dissociated retinal cells taken at stages before optic fibers grow across the tectum have been shown to adhere preferentially to the appropriate tectal half (Barbera, Marchase, & Roth, 1973). It may be noted that a similar result was obtained using pigment epithelial cells, thus lending credence to the suggestion (Sperry, 1944) that the specificity of the ganglion cells may derive in part from this epithelial tissue, not only when the retina is experimentally induced to regenerate from pigment epithelium, but also during normal development. The misdirected optic fiber growth seen in various albino mutants also suggests a similar link between epithelial and neural tissue (see Section VIII on plasticity in mammals).

IV. Tectal Lesion Experiments

Additional support for the sliding-scale interpretation came from experiments in goldfish (Fig. 3) in which it was found that surgical ablation of the caudal half-tectum led to an orderly compression of the whole retina onto the remaining rostral half-tectum (Gaze & Sharma, 1970). These results were generally confirmed and extended in electrophysiological studies in goldfish by Yoon (1971, 1972a) and Sharma (1972a, 1972b). Like the compound-eye experiments, these also were open to explanation on the grounds that a developing tectal field cut in half may undergo self-reorganization into a whole field. This would be expected without question in embryonic stages and might conceivably be possible in juvenile stages in goldfish in which the tectum and retina are still growing (Kirsche & Kirsche, 1961; Meyer, 1974). While such a late regulation would be surprising (Meyer & Sperry, 1973, 1974), to dismiss this possibility *a priori* (Gaze, 1974) is incautious, especially in view of the evidence on retinal specification in Amphibia indicating that these locus specificity properties can regulate well after many other cellular properties have ceased to be affected (see Hunt, 1975, and Section III on eye specification).

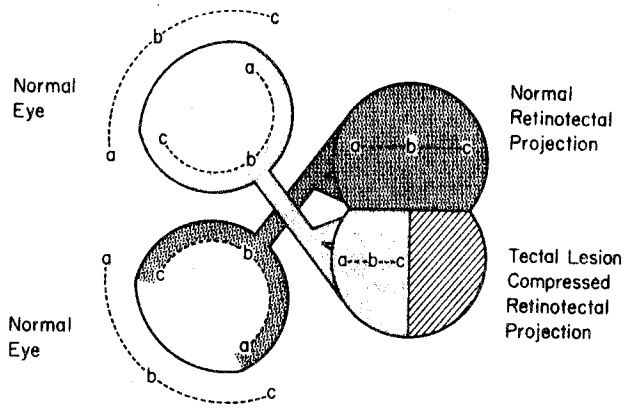

FIG. 3. Diagram of the visual field and retinotectal projection obtainable in a juvenile goldfish several months following either caudal tectal ablation, as indicated by the slashed region, or insertion of a mechanical barrier between rostral and caudal tectal halves.

Similar tectal ablations in adult tree frogs, *Hyla regilla* (in which tectal growth was complete), gave results consistent with an interpretation in terms of field regulation. Compression of the sort obtained in goldfish failed to occur (Meyer & Sperry, 1973). Electrophysiological mapping at various times after surgery showed little significant change in retinotectal projection even with combined section and regeneration of the optic nerve. Similar results have been reported also for *Xenopus* (Straznicky, 1973). Behavioral perimetry mapping in *H. regilla* demonstrated little or no recovery from the initial scotoma produced by the tectal ablations. Additional behavioral evidence indicated that optic fibers corresponding to the ablated tectum grew out of their usual course all the way to the appropriate symmetric synaptic zone of the contralateral tectum rather than terminating inappropriately in the rostral tectum. This growth to contralateral symmetric sites, however, was not responsible for the absence of compression, since compression also failed to occur after bilateral ablations (Meyer & Sperry, 1973). The results in adult tree frogs seemed to rule out the view that tectal terminations depend on relative positioning of fibers within available target areas in favor of tectal regulation.

Similar explanations involving reorganization of tectal specificities have also been advanced by other workers (Gaze, 1974; Hunt & Jacobson, 1973b; Yoon, 1971). However, several more recent studies designed to further test this interpretation indicate that tectal regulation may not be the principal answer (Meyer, 1975a, 1975b). Other explanations are now seen that can account for these plasticities in a manner compatible with chemoaffinity concepts. Before turning to these we need to consider certain gaps in the published evidence.

A. Contradictions and Gaps in the Evidence

The lack of compression originally reported by Jacobson and Gaze (1965) after full-length medial or lateral tectal ablation and optic nerve crush has not been satisfactorily reconciled with Yoon's (1971) demonstration of mediolateral compression after removal of only the caudal quadrant (see Introduction). Optic tract interference consequent to full length lesions has been invoked as an explanation but appears from autoradiographic evidence (Meyer, 1974) to be insufficient to prevent fibers from reaching the tectum. It remains possible, however, that the regenerating fibers initially reestablish an uncompressed projection and only slowly undergo compression over a period substantially longer than was allowed by Jacobson and Gaze. When 18 months were allowed for recovery after surgical ablation of medial tectum (Meyer, unpublished), electrophysiological mapping showed clear evidence of the predicted compression. A similar time-dependent plasticity for the rostrocaudal dimension suggested in other work was either considered inconclusive (Gaze & Sharma, 1970) or, involved a disruption of the normal optic pathways and a more complex double remnant preparation (Sharma, 1972b). Accordingly, a further study was undertaken, as described below.

A series of 5–11 cm fish sustaining caudal tectal ablations were studied electrophysiologically at 44–214 days after optic nerve interruption. A more accurate eye-in-water recording technique (Meyer, 1974) was employed after comparison with the eye-in-air method revealed several deficiencies: Eye alignment in air by retinal landmarks is much more difficult. The extreme myopia of some 50 diopters (Wartzok & Marks, 1973) results in receptive fields that are 5–10 times larger than normal (Cronly-Dillon, 1964; Jacobson & Gaze, 1965; Schwassman & Kruger, 1965; Yoon, 1971). In addition, an artifactual enlargement of the visual field representation was found that could mask field defects (Meyer, 1974).

Recordings taken at up to 2–3 months showed a relatively uncompressed visual field with a large posterior scotoma, while at longer periods the virtually complete compression previously reported (Gaze & Sharma, 1970; Yoon, 1971, 1972a) was confirmed. Thus, even in this plastic system, the evidence indicated the directive influence on fiber growth of specific position dependent affinities that must be accounted for in any comprehensive model.

Disagreement exists also on the effect of a surgical incision separating the rostral from the caudal tectum. Reversible full-field compression of the rostral half was found by Yoon (1971, 1972a) after simple transection or incision with insertion of Gelfilm. This compression was not found by Sharma (1972b, 1972c) after incisions even when combined with ablation of

surrounding tissue. Contrary to Yoon and all available anatomical evidence, Sharma (1972b) further suggested that innervation of the caudal tectum may not be completely disrupted by such lesions. Arora (1973) found that these procedures did interrupt optic fibers, but, in contradition to both Yoon and Sharma, he reported that fibers once cut were unable to regrow across the tectal incision.

In an autoradiographic study (Meyer, 1974), transverse mediolateral incisions across even small regions of the dorsal tectum were found to disrupt virtually the entire innervation posterior to the lesion. After several months the posterior innervation became reestablished by fiber growth through the incision site. Even when a 500-μm-wide ablation was made between the rostral and caudal tectum, similar regrowth was eventually found penetrating the glia-filled scar.

In view of this ready growth across tectal incisions, Yoon's (1971) compression after incision seems surprising, but his sketches indicate the possibility of rather extensive tectal damage, which may have been sufficient to block fiber growth. In subsequent experiments more refined incisions did not produce compression (Yoon, personal communication), and insertion of a barrier was required (Yoon, 1972a). In this context the fine incisions of Sharma would not be expected to produce compression, and in those experiments involving midtectal ablations where compression was expected, the 5–11 months of postoperative recovery may have been long enough to permit the kind of reversal of compression found by Yoon (1972a).

In summary, the kind of tectal separation that has thus far produced compression involves a sustained interruption of tectal continuity and blockage of fiber growth. Since compression now appears not to be a consequence of an autonomous field-type regulation of tectal cytospecificities, the subsequent expansion of the projection following an incision-induced compression (Yoon, 1972a) could be a result of optic fiber regrowth across the incision to preferred sites of termination—the release of a forced and unstable condition. The autoradiographic data showed further a rather strong growth preference of the optic fibers to return to their correct laminae in the tectum within a few hundred micrometers after deflections in traversing the incision scar.

According to Yoon (1971, 1972a), posterior tectal ablation results in a uniform compression, whereas Gaze and Sharma (1970) and Sharma (1972b) found that part of the displaced map generally came to be superimposed on the remaining projection. This discrepancy remains unexplained. Until the relevant factors are understood, it may be more profitable to focus attention on the experiments involving optic nerve interrruption, which is probably more directly relevant for development.

The studies showing compression have relied almost exclusively on

electrophysiological measurements presumed to come from the presynaptic terminal arbors of the optic fibers. This gives no direct evidence of functional synaptic connectivity. Recently Scott (1975) has succeeded in training hemitectal goldfish to discriminate visual stimuli presented to restricted regions of the visual field. Preliminary results indicate that vision is eventually restored within the original scotoma in an orderly progression that moves posteriorly from the anterior scotoma border. Her results suggest that the compression that has been mapped by electrophysiological recording from presynaptic optic terminals involves a correlated formation of tectal synapses and so represents a genuine reorganization in functional connectivity.

In contrast to previous results in *Hyla* (Meyer & Sperry, 1973) and *Xenopus* (Straznicky, 1973), significant, though apparently limited, compression of tectal projection has been recently found in *Rana* (Udin, personal communication). A consequent reinvestigation in *Hyla* with modified techniques indicates some possible signs of compression, but these seem to be much more limited than reported in *Rana* (Meyer, unpublished). Whether this represents a possible species difference or technical and procedural differences is not clear. It is worth noting, however, that interpreting small changes can be problematical. In frogs, terminal arbors of some fibers are several hundred micrometers long and the extent of dendritic arbors of some tectal cells is even greater (Maturana, Lettvin, McCulloch, & Pitts, 1960).

B. Latest Findings Countering Autonomous Field Regulation

In an autoradiographic study aimed at testing regulation (Meyer, 1975a), prior removal of a caudal half-tectum was combined with lesion of either a nasal or a temporal helf-retina and optic nerve crush. In the control, where a nasal half-retina grew onto the noncorresponding rostral half-tectum, a caudal bias of reinnervation, expected regardless of regulation, was found present up to 5 months after surgery. In fact, the caudalmost labeling was heavier than normal even spreading vertically beyond the usual confines of the normal terminal layers. At first sight this contrasts with similar electrophysiological studies (Horder, 1971; Yoon, 1972b) in which even topographic spreading was reported, but it is in line with Roth's (1972) Bodian study. Difficulty in electrically probing the downcurved rostral extreme of the tectum (Meyer, 1974) may help to mask the asymmetry of innervation as revealed by autoradiography.

According to the control findings, the innervation from a temporal hemiretina ought to be similarly biased toward the rostral end of the tectal remnant if tectal respecification occurs. If respecification does not occur, reinnervation ought to spread evenly across the entire tectal remnant. Autoradiography as late as 3–5 months after nerve crush gave little indica-

tion of any asymmetry in the distribution of terminals but rather showed evenly spread label across the entire rostrocaudal extent. The same result was also obtained in other cases following the same surgery when the optic nerve was recrushed after 5 months. These findings strongly discount the primacy of a developmental field type reorganization of tectal specificities in response to the lesion.

Preliminary electrophysiological evidence reported by Cook and Horder (1974) is also counterindicative of field regulation. They confirmed that the initial recordable projection which grows onto a half-tectum shows only limited compression, thus giving rise to a large posterior field scotoma. After allowing sufficient time for the completion of compression, the optic nerve was recrushed. Again, the initially regenerated map was found to lack a large part of the posterior visual field. Since a significant extent of initial fiber growth takes place in the optic nerve and tract and within the parallel layer of the tectum (Attardi & Sperry, 1963; Horder, 1974; Roth, 1972), the above result with electrical mapping taken alone might simply mean that the initial guidance of fiber growth is not subject to tectal regulative changes controlling termination in the plexiform layer. Taken together the autoradiographic and electrophysiological evidence seems to contraindicate any automatic and stable lesion-induced respecification of the tectum.

C. Selective Deflection of Fascicles of the Optic Radiation

Chemoaffinity and other growth-regulating factors were implicated in an experimental series involving intertectal transplantation of fascicles of optic fibers (Meyer, 1974, 1975b). When selected fascicles of fibers (roughly 10–15% of the total tectal complement) were dissected free of the dorsal tectum and inserted into the contralateral tectum denervated by prior eye enucleation (Fig. 4), autoradiography and electrophysiology at up to 8 months indicated that these deflected fibers had spread over several times

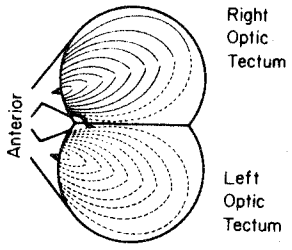

FIG. 4. Simplified diagrammatic representation of the course of optic fiber fascicles across superficial tectum. Select fascicles, such as those normally occupying the region indicated by the dashed lines on the right optic tectum, were cut free of surrounding tectum, deflected across the midline, and inserted into the anterior end of the opposite tectum, which in this case, was denervated by prior eye enucleation indicated by dashed lines on the left optic tectum.

more tectal area than normal, centered roughly on their appropriate territory. When a similar surgical deflection of fibers was carried out on a normally innervated tectum, the transplanted fibers came to occupy, in patchwork pattern, roughly the correct region of contralateral tectum. Surprisingly, however, these tectal areas were often found to be exclusively occupied by the deflected fibers, even though severed normal fibers with presumably identical specificities were intermixed in the same regenerating system. This segregation occurred regardless of whether these normal fibers were left intact, suggesting active displacement of existing fiber terminals, or whether they were temporarily disrupted by a transverse incision across the rostral tectum. This latter exclusivity in occupation of local tectal regions was confirmed by electrophysiological mapping. These recordings additionally suggested that compression and other topographic distortions may occur under these conditions, which would further indicate that tectal regulation, ruled out in these experiments, is not necessary to explain these kinds of plasticities. A place preference was simultaneously evidenced by the tendency for these transplanted fibers to grow toward appropriate regions even when inserted into inappropriate tectal areas. In addition to chemoaffinity attraction between retinal and tectal elements, other factors are indicated, such as interfiber competition for available terminal territory.

In the above fiber deflection studies, there was some suggestion that intermixing of fibers can be promoted by manipulating the order and timing of ingrowing fibers or by misrouting fibers at the chiasm instead of at the rostral tectum (Meyer, unpublished). Differences in these experimental variables may possibly explain why segregation was not reported in previous lower vertebrate work involving dual optic input onto one tectum (Arora, 1966; Gaze & Keating, 1970; Sharma, 1973; Straznicky *et al.*, 1971). However, the possibility that this could have been simply missed is supported by results of a replication of Sharma's (1973) goldfish experiment, where, after unilateral tectal removal, optic fibers miscrossing to the opposite tectum appeared by autoradiography to displace, in places, the existing normal optic innervation (Meyer, unpublished). In a recent fiber deflection study Cronly-Dillon and Glaizner (1974) also found electrophysiological evidence suggestive of such displacement of normal innervation. However, the low success rate (2 of 23 fish), the possibility of optic nerve damage during retinal surgery, and the minimal effect indicated by their published map make interpretation difficult.

D. Interpretation of Retinotectal Compression

Taken together, the preceding experiments argue against field regulation (Meyer & Sperry, 1973), or any similar intrinsic reorganization of tectal gradient specificities (Gaze, 1974; Hunt & Jacobson, 1973b; Yoon, 1973)

as the main cause of topographic compression or decompression. Some initial forced mismatching of presumably specified retinal and tectal elements would seem to be necessarily involved. In addition to mechanical and other chemical effects universal to nerve growth and connection, influential operative factors must presumably include a general terminal-junction-seeking growth pressure of unconnected optic fibers; homeostatic denervation and synaptic saturation effects; chemoaffinity interactions, including those among retinal fibers as well as between retinal and tectal elements; and competitive effects between normally overlapping fibers with preferential affinities. The picture of terminal patterning that emerges from the available evidence suggests preferential but not obligatory affinities for appropriate tectal elements, the fibers in their home territory being more effective competitors than more foreign fibers.

Recent electrophysiological, anatomical, and autoradiographic observations on half-tectum goldfish at successive stages of compression (Meyer, 1974) indicate a progressive abnormal thickening around the outer plexiform layer (main termination layer) that starts along the lesion border and then extends rostrally throughout the remnant half-tectum and is correlated with electrophysiological and behavioral evidence of compressed remapping (Scott, 1975). This evidence for a gradual caudorostral progression of compression across the tectum, along with other data, suggests an explanation along the following lines: After tectal ablation, say of the caudal half, and crush of the optic nerve, fibers from temporal retina tend to regrow by chemoaffinity guidance along proper pathways to their appropriate normal terminal zones on the rostral remnant, where they begin to form terminal arborizations and synaptic connections. Axons from the nasal retina, deprived of their preferred termination, on the other hand, continue a pressured exploratory growth, piling up near the caudal edge of the intact half-tectum. As the temporal fibers continue to arborize rostrally, forming a relatively uncompressed projection, the deprived exploratory nasal fibers tend to be increasingly excluded from rostral regions by the reduction in available terminal sites and in the stimulating effect of denervated tissue. These nasal fibers would thus be generally pressured toward the caudal border, their nearest chemoaffinity match and most competitive position. The nasal axons that normally terminate just caudal to the lesion border, however, would be nearly as competitive in chemical gradient terms as the nasal fibers just rostral to the lesion, and in addition would have extra competitive growth potency by virtue of their lack of other target cells. Since the number of synaptic sites is limited, the foregoing effect would pressure the adjacent temporal fibers to be displaced further rostrally, which in turn would displace fibers rostral to them, in domino fashion. Subsequently, with ever more nasal fibers filling in from the caudal edge, this sequence

would continue until a fully compressed projection is achieved. At this point the driving force for compression, deprived fibers seeking terminal sites, is mitigated, with the retinal fibers having made what might be thought of as the best available matchings.

Chemoaffinity attractions between fibers from the same retinal regions may also contribute importantly to this topographic ordering (Meyer, 1974, 1975b). This interfiber affinity is conceived to operate not only between the growth cones and shafts of fibers growing down the nerve and transversing through the parallel layer of the tectum, but also between the growing terminals and terminal arbors of fibers within the plexiform layer where termination occurs. The increase of fiber surface area resulting from these terminal arborizations would be reasonably expected to increase such interfiber interactions. The tendency of fiber endings to aggregate near like fibers would work in itself to preserve and refine the topography with some independence of the precise position of fibers on the tectum. Retinotectal affinities would, of course, still be required for overall topography and general orientation of the projection.

The progressive remapping process may include a further important factor, namely, a modulatory shift in tectal cell specificity dependent upon, and maintained by, chemical influences from the regenerated retinal fibers. It has been generally presumed that the tectal cell specificity determining preferential affinity for synapsis depends on the combined effect of intrinsic and extrinsic factors coming, respectively, from the cell's own chemical synthesis on the one hand and from different chemical inputs from surrounding cells on the other. It is possible that the latter extrinsic factors may include chemical products transmitted from the retinal fiber terminals or related contact-mediated changes, like those recently postulated to occur during development (McMahon, 1974). Accordingly the extra growth pressure for synapsis along the lesion border in target-deprived axons that causes these fibers to synapse on near-match cells, as described above, would result in the transmission of slightly off-match extrinsic specificity products. These can be conceived to shift slightly thereby the overall specificity properties of the tectal border cells involved. This slight caudal shift of specificity (with a posterior lesion) would allow adjacent, even more caudal, unconnected fibers to synapse on the affected tectal cells, which in turn would further shift the cell's specificity in the caudal direction and permit acceptance of still more remote caudal retinal fibers. Logically this process would continue progressively until eventually fibers even from the far distant border of the lesion are accepted at the lesion edge, and the successive progressive shifts rostrally across the remaining intact tectum reach a stable equilibrium. It may be noted that this model for the shifting of fiber projections does not involve a functional breakdown. The shift from one set

of afferents to another on each cell is accomplished gradually through progressive intermediate stages.

This interpretation suggests further that the scotoma would not become functional in a random or chaotic manner, nor in a general overall return first of faint, then stronger, vision throughout the missing half-field. On the above terms vision should return first along the anterior margin of the scotoma and then spread progressively backward toward the posterior periphery. This latter pattern of visual return is what seems to be demonstrated in the early data of Scott (1975) on behavioral mapping of compression by conditioning techniques with the optic nerve intact. The molecular machinery of each cell along a developing gradient must logically synthesize an intermediate average of the extrinsic chemical inputs received from adjacent cells on opposite sides. Any input specificity transmitted through afferent terminals as proposed here would presumably be weighted also in the established averaging process of these mature neurons or in its end products, in order to change the effective chemospecificity of the cell. Such considerations become important in setting the requirements and limitations for molecular models.

The foregoing represents the best interpretation for retinotectal compression we can see at present with existing evidence. Obvious uncertainties remain. It assumes that the individual optic fibers and tectal neurons are chemically specified according to the field position of their respective cell bodies, that orderly preferential contact affinities exist between the optic fibers and the tectal neurons, that these may be shifted by abnormal growth pressures, that the selective preferences for topographic mapping have their genesis in developmental field gradients and are gradient-structured, and that related axial gradient specificities exist throughout the brain and entire body which help determine the afferent pathways of fiber growth as well as central synaptic termination. It has never been claimed that these cytochemical affinities are exclusive or rigid or are the *only* factors regulating nerve growth and connection, and it has repeatedly been emphasized that the exact way in which they are expressed can be expected to vary in detail in different systems, different species, growth stages, and under different pathological and experimental conditions. It seems rather improbable that the mechanisms for topographic compression evolved to cope with such gross nervous system damage as produced in these experiments, and more likely that they are a secondary effect of certain demands of development.

In sum, the plastic reorganizations that follow tectal lesions are not only compatible with chemoaffinity concepts, but some of the observed effects, such as the initial specificity exhibited by optic fibers growing onto a half-tectum and the asymmetry of reinnervation following noncorresponding retinal and tectal lesions, directly support the idea of matching retinotectal

preferences. These remapping phenomena, however, do bring to light the presence of additional competitive-type factors that importantly determine fiber growth and connectivity.

V. Retinal Lesions

Perhaps the most convincing and direct evidence for the chemoaffinity model has come from the retinal eye lesion experiments. With a modified Bodian stain selective for regenerating fibers, Attardi and Sperry (1963) showed in goldfish that different sectors of retinal field regenerate different and appropriate tectal projection patterns when the rest of the retina is removed (Fig. 5). The selective tectal termination was shown also with electrophysiological methods in a gross evoked potential study of tectal innervation following large retinal ablations (Westerman, 1965) and by a microelectrode recording experiment using a hemisected optic nerve preparation (Jacobson & Gaze, 1965). Similar selective tectal innervation has been demonstrated also in chick embryos by eye ablations prior to optic nerve outgrowth with a variety of anatomical techniques (Crossland *et al.*, 1974; De Long & Coulombre, 1965).

More recent work on goldfish, however, seems to introduce some complications and discrepancies into this simple picture. A Bodian study by Roth (1972), though showing hemiretina innervation to be predominantly selective, suggested that this innervation may extend somewhat into inappropriate regions. A more serious discrepancy is found in Horder's report (1971)

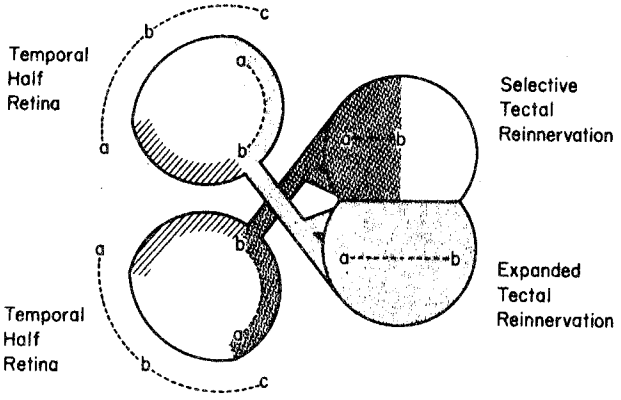

FIG. 5. Diagram of the visual field and retinotectal hypothetical projections in juvenile goldfish showing an example of rigidly selective innervation on one tectum or completely expanded reinnervation on the other tectum following optic nerve crush and lesion of nasal half-retina as represented by the slashed region.

that an isolated nasal retina spreads electrophysiologically across the entire tectum, although the tectal projection from temporal, dorsal, and ventral hemiretinas under the same conditions remained restricted selectively to the appropriate half-tectum. Even more plasticity was found in Yoon's unit-recording study (1972b), where both a nasal and a temporal half-retina were reported to have spread over the entire tectum (Fig. 5).

However, some important methodological differences between these apparently conflicting studies precluded definite conclusions. The findings showing substantial plasticity were based on relatively long postoperative survival periods, leaving the possibility that the optic fibers may have first grown to their appropriate regions and only later spread into other adjacent areas. This would be analogous to the changes in the regenerated optic projection seen after removal of the caudal half-tectum. Expected optic aberrations in the ocular system caused by the eye surgery may have produced measurement errors, and the discrepancy between these electrophysiological studies might be accounted for in these terms. Additionally, almost no systematic histology has been done in any of the above work to verify the size of lesion or the possibility of retinal regeneration, which was found to be quite extensive in the original Attardi and Sperry (1963) study.

Some of these potential complications were taken into account in a recent autoradiographic study (Meyer, 1975a, 1975b). At various periods after combined optic nerve crush and nasal or temporal retinal lesions made by several procedures, complete serial sections of both retina and tectum were taken. In general the resulting innervation was found to be preferentially but not rigidly selective (Fig. 6). There was some indication that the spread into

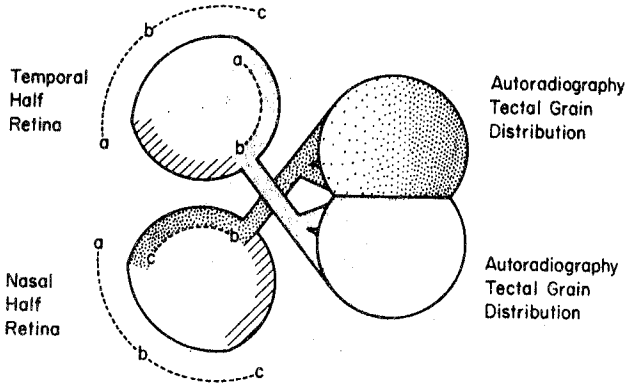

FIG. 6. Diagram of the initial selective tectal reinnervation indicated by the autoradiography studies on goldfish in which optic nerve crush was combined with lesions of either nasal or temporal half-retina as indicated by the slashed region.

foreign regions was greater with longer survival times, which may partially explain the differences in previous studies. While some of this apparent spreading may only reflect retinal regeneration that was quite significant in some cases, especially at long survival periods, terminal spread was evident in many animals where retinal regrowth was minimal or absent.

Reinnervation was most selective following nasal lesions, after which the appropriate rostral tectum was densely innervated and the caudalmost tectum hardly innervated at all. However, instead of the abrupt drop-off at the margin seen in controls, a gradientwise decrease in labeling was found to extend well into the caudal tectum. This attenuated spread that was evident in autoradiography may simply have gone undetected in previous studies which relied on electrophysiology or less sensitive anatomical methods, though some indication of spread was seen in Roth's (1972) Bodian study. The results do not conform with the electrophysiological evidence of Yoon (1972b) showing complete uniform expansions of a temporal half-retina. However, use of Yoon's lesion method, transcleral electrocoagulation, was found in the autoradiography studies to produce not only somewhat variable retinal destruction, but also extensive damage to the outer layers of the eye, resulting in gross morphological changes in eye structure and optics. Consequent measurement errors and the possibility that the recordings were from postsynaptic tectal cells (Yoon, personal communication) raise doubts about the exact retinal origin and tectal disposition of optic terminals in his study. Thus, it appears safe to conclude that fibers from the temporal half-retina exhibit strong, though not rigid, preference for the appropriate tectal half. This conclusion presumably applies as well to a dorsal or ventral half-retina, on which the literature is in reasonable agreement.

In the case of the nasal half-retina, the autoradiography indicated a lesser degree of selectivity. When more than 35–40% of the temporal retina was destroyed, the appropriate caudal regions of the tectum were more heavily innervated than the rostral area, but substantial rostral spread of labeling even to the extreme pole was often evident. When temporal eye lesions were smaller than about 35%, no difference between rostral and caudal grain densities were discernible several weeks after initial fiber ingrowth. Again, this contrasted with controls labeled immediately after eye lesions, where only light labeling of fibers of passage was seen in the rostral tectum. Thus, the view we get of the retinal lesion effects from the present evidence is an intermediate one supporting marked selectivity, but not as strict in goldfish as initially appeared.

An impressive high degree of selectivity has been demonstrated recently in Bodian stain (De Long & Coulombre, 1965) and autoradiographic studies (Crossland *et al.*, 1974) on developing retinotectal projection in the chick following embryonic eye lesions. Some slight spreading may be indicated

in the 300–500 μm transition zone from heavy labeling to background, which appears wider than might be expected for the normal projection. In the chick experiments fibers were clearly seen to bypass uninnervated foreign tissue en route to their appropriate sites, but as in goldfish, there was some suggestion that spreading was greater under these conditions. Since the retinal ablations preceded optic nerve outgrowth in these chick studies, the selectivity cannot be attributed to the presence of previous optic fibers. The suggestion that remnants of prior fiber channels confound the goldfish work (Jacobson, 1970) appears contraindicated by the chick data and also by the fairly rapid terminal and axon degeneration seen to follow nerve section in goldfish (Roth, 1972).

The evidence from juvenile goldfish points against the presence of embryonic field regulation of retinal remnants (Meyer & Sperry, 1973) or other postulated respecifications of retinal elements (Gaze, 1974; Hunt & Jacobson, 1974; Yoon, 1973). While conceivably some kind of complex partial regulation could explain the kind of expansion observed from a goldfish nasal hemiretina, such regulation is incompatible with the selectivity of innervation from temporal, dorsal, and ventral hemiretinas. These data, like those from half-tectum experiments, seem better explained in terms of chemoaffinity operating in combination with other general growth factors, e.g., a tendency for regenerating fibers to make use of available space and the biochemically stimulating effect of denervated tissue.

VI. Pathway Patterning

While the distribution of optic terminals on the tectum has been the subject of much experimentation, factors affecting the growth and structure of the optic pathways leading to the site of termination have received relatively little attention, perhaps partly because the usual behavioral and electrophysiological methods rarely give this information. In an anatomical study on goldfish, Attardi and Sperry (1963) first demonstrated by Bodian staining that fibers regenerating from retinal remnants preferentially select appropriate afferent routes through the optic tract and across the tectum to terminal tectal sites. They accordingly extended the chemoaffinity theory to include patterning of central fiber tracts, and proposed that the chemotatic patterning is regulated by biochemical specificities similar to those governing synapsis. These findings have been in part confirmed by Roth (1972) and extended recently to the optic nerve itself where, after disrupting nerve crush, the intricate retinotopic organization was found by both light (Roth, 1974) and electron microscopy degeneration techniques (Horder, 1974) to be reformed by the selective regrowth of optic fibers. In chicks, pathway

selectivity through the tectum has also been observed in eye lesion experiments (Crossland *et al.*, 1974; De Long & Coulombre, 1965). More direct evidence that this organization involves an active preferential selection of pathways comes from experiments in which the medial and lateral brachia of the optic tract have been surgically crossed (Arora & Sperry, 1962). Abruptly redirected fiber growth toward the appropriate pathway resulted.

While pathway patterning undoubtedly contributes to the formation of topographical termination, it alone is insufficient and, in some cases, not even necessary for orderly innervation. The fan-shaped spreading of optic fibers across the tectum from peripheral entry points means not only that most fibers must grow past inappropriate tectal sites but also that different fibers growing in virtually identical paths terminate in different regions. In the optic nerve of *Rana*, fibers appear to be randomly distributed (Maturana *et al.*, 1960), and perhaps partially as a consequence, the initially regenerated retinotectal map is quite disorganized (Gaze & Jacobson, 1963; Gaze & Keating, 1970). Despite this, good retinotopic order is eventually restored (Gaze, 1959; Maturana, Lettvin, McCulloch, & Pitts, 1959). Even when fibers are surgically forced into abnormal paths, such as through the oculomotor nerve root (Gaze, 1959; Hibbard, 1967) or through dorsal cranium (Hibbard, 1959; Sharma, 1972d), appropriate termination tends to be achieved.

In goldfish there has been some suggestion from early behavioral (Sperry, 1951a) and anatomical work (Roth, 1972) that fiber guidance during regeneration is imperfect. Further recent evidence indicates that regenerating optic fibers may find their correct terminal sites in the dorsal tectum via quite abnormal routes outside even the medial brachium (Horder, 1974; Meyer, 1974). It should be emphasized, however, that most fibers in these studies, unless surgically prevented, did grow along or near their normal routes in accordance with previous evidence (Attardi & Sperry, 1963; Horder, 1974; Roth, 1972, 1974). Even in the anatomical studies where incorrect routes were surgically forced, a tendency of fibers to reestablish their appropriate pathways could be observed (Arora & Sperry, 1962; Hibbard, 1959, 1967). This orderly growth can be explained by chemoaffinity attraction between optic fibers and the cytochemically tagged elements, neural and nonneural, distributed along the optic pathway (Sperry, 1965a). It is inferred (Sperry, 1965a) that the cell surface membranes throughout the developing embryo, in all tissues, acquire cytochemical specificity labels. Selective affinities between optic fibers from contiguous retinal loci might also contribute to topographical order, but this interfiber interaction alone cannot explain the orientation of the topography relative to the rest of the nervous system. There is some suggestion that regenerating fibers have a tendency to grow into inappropriate neighboring routes after retinal

lesions (Roth, 1972). This may be analogous to the expansion seen in the tectal innervation and suggests that the same kinds of factors may also operate in route selection.

VII. Tectal Gradients and Polarity

The inferred cytochemical polarization of the optic tectum and its postulated role in regulating the topography of retinal projection has not gone unquestioned and untested (Crelin, 1952; Jacobson, 1970; Levine & Jacobson, 1974; Sharma & Gaze, 1971; Stone, 1960; Yoon, 1973). The logical necessity for such has long been evident in view of a substantial array of experimental observations that seem to be accountable only on these terms. Crelin (1952) performed surgical rotations of the tectum of *Ambystoma* at different stages of development and later tested the resultant orienting responses. These were normal after early rotations but with late rotations became so confused as to be difficult to interpret. In more recent experiments on adult goldfish (Sharma & Gaze, 1971; Yoon, 1973) and postmetamorphic froglets (Levine & Jacobson, 1974), a rectangular piece of tectum comprising 10–20% of the total tectum was excised and reimplanted in rotated positions, breaking all optic connections in the process. In most instances where reinnervation of the implant was successful, its projection pattern was found to be correspondingly rotated (Fig. 7) with respect to the normal surrounding area. A substantial histological gap between the

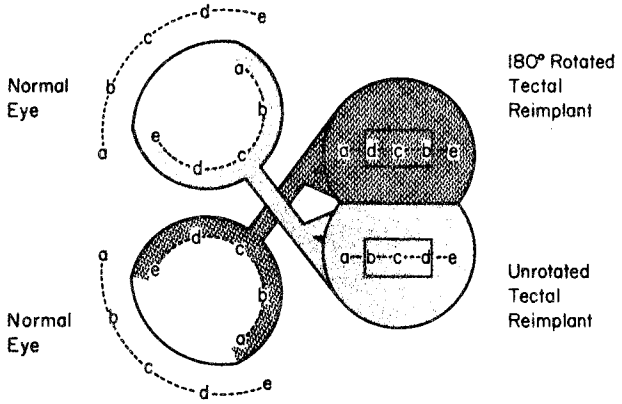

FIG. 7. Diagram of the kind of visual field and retinotectal projections in goldfish several months after excision of the indicated piece of central tectum and reimplantation in 0° or 180° rotated position (Levine & Jacobson, 1974; Sharma & Gaze, 1971; Yoon, 1973).

rotated tectal implants and the surrounding tectum has been shown both histologically and electrophysiologically that tends to isolate and insulate the reimplants and probably helps to preserve their intrinsic polarity, especially in goldfish. In the frog, this discontinuity eventually comes to be much less evident, but a significant gap may be present during the initial reinnervation of the implant. The absence of insulating reactions around tectal implants may account for the exceptional normal, unrotated projection onto rotated implants as observed in several frogs of Levine and Jacobson (1974). While the results further affirm the presence of cytochemical polarity and its importance in chemotactic guidance of fiber growth and termination, to argue that the extensive previous evidence has been ambiguous (Levine & Jacobson, 1974) seems unwarranted. The suggestion that the polarity of the tectum may be imposed initially during development by the ingrowing optic fibers (Jacobson, 1970) appears incompatible with the early eye rotation and other related observations.

VIII. Plasticity in Mammals

In the development of the retinogeniculate system in higher mammals, the requisites for cytochemical specificity and interneuron affinity in patterning of nerve pathways and connections appear to reach a peak in refinement, complexity, and precision, particularly in man, where close to one million optic fibers connect to about one million geniculate neurons in what appears to approximate a cell-to-cell relation (Polyak, 1957). Developing optic fibers advancing into the primate lateral geniculate nucleus must presumably carry cell-specific chemical labels to select for the latitude and longitude of specific target cells, not only in one central geniculate map, but among six separate maps arranged in laminar fashion, each map in register with the others. After finding the correct terminal locus in the correct one of the six layers, the invading retinal fibers must then make further selections among the types of neurons present, according to their specifications for color discrimination and other differential functions involved in feature detection, on–off, off–on, and luminosity effects. Most or all of these various selectivities expressed in geniculate synapses must also be extended and preserved among the system of geniculostriate synapses in the visual cortex.

There is much to suggest that chemoaffinity mechanisms similar to those indicated for lower vertebrates are responsible also for the developmental organization of the more elaborate visual pathways of mammals. However, the experimental conditions are more complex, and the developmental stages at which mammalian experiments are feasible and the kinds of sur-

gical intervention are, of course, much more restricted. Because of the limited regenerative capacity in mammals, work on mature individuals has been largely confined to analyses of preterminal and collateral sprouting. Virtually nothing has been done on initial specification since eye development and optic nerve outgrowth are already far advanced in the neonatal placental animals that have been used to date.

This difficulty is circumvented in part in studies of genetic alterations of the visual system, as in albinos and particularly in Siamese cats. In the latter, for example, correlated with their cross-eye characteristic, a large section of temporal retinal fibers cross at the chiasm instead of growing to their usual ipsilateral geniculate layers (Guillery, 1969). Despite this abnormal path, the contralateral geniculate termination of these aberrant fibers is in the temporal fiber layer and in the order that would be expected from a chemoaffinity matching scheme for the retinogeniculate system (see Sperry, 1965). Contrary to a previous report (Berman & Cynader, 1972), the retinocollicular projection now also appears to be in accord with this kind of scheme (Lane, Kaas, & Allman, 1974). Although the geniculocortical topography seen by Kaas and Guillery (1973) similarly conforms with such a matching scheme, that recorded by Hubel and Weisel (1971) in another strain of Siamese cat (Kaas & Guillery, 1973) appears to present differences, and further evidence is needed before these disparities can be resolved.

Other relevant studies have involved various visual system lesions in neonatal animals where at least some optic axons are still capable of substantial growth. Lund and Lund (1973), for example, made small eye lesions in rat pups and found anatomical evidence in the mature animals that the projection of the lesioned eye to the superior colliculus contained a small correspondingly placed denervation zone. Surrounding fibers apparently failed to invade these areas, but fibers from the other eye, tentatively presumed to be homotopic to those destroyed, sprouted or changed course at the chiasm to find the denervated loci. However, the precise retinal origin and organization of this abnormal ipsilateral projection requires further elucidation.

In a series of experiments on newborn hamsters, unilateral removal of the superficial gray layer of superior colliculus (the site of the optic projection) has been found to result in hyperinnervation of the dorsal terminal nucleus of the accessory optic tract of the same side by optic fibers presumably destined for the missing collicular site. Many more fibers, however, grow across the lesioned colliculus to terminate in the opposite superior colliculus (Schneider, 1973). These aberrant fibers apparently select bisymmetric mirror target sites as shown behaviorally in the same kind of left–right reversal of visual responses that appear after crossed tectal innervation in amphibians (Sperry, 1945, 1951a). Excluding for the moment areas

directly damaged or denervated, the displaced optic fibers innervate only those regions where optic fibers normally terminate. If the collicular lesion is restricted to the rostral half, compression onto the caudal remnant is indicated by recent Fink–Heimer studies (Schneider & Jhaveri, 1974). Provided subsequent electrophysiological studies confirm that an orderly compression is acquired, this would appear analogous to the goldfish half-tectum experiments and similar arguments would apply.

Behavioral tests on hamsters give tentative indications that the retinotopic order of aberrant crossed optic fibers is not as refined as normal (Schneider, 1973). However, in neonatal mammals only a few weeks of significant fiber elongation appear available for corrective growth after surgical intrusion (Kalil, 1973; Lund, Cunningham, & Lund, 1973). By contrast, in goldfish several months of regeneration seem to be required for stabilization of the retinotectal projection following simple nerve crush (Meyer, 1974; see above). The minor growth errors seen after collicular ablation in hamsters may in part reflect limitations in the quality and duration of plastic optic fiber growth in these animals.

Another approach has involved surgical denervation of areas contiguous to retinal projection sites. One of the simplest experimental designs consists of removal of one eye at various periods after birth (Kalil, 1973; Lund & Lund, 1971; Mathers & Chow, 1973). Resultant central denervation is most marked contralateral to the enucleation. Substantial abnormal invasion of the denervated areas can be seen to result anatomically in the lateral geniculate and in superior collicular regions normally occupied by the absent contralateral fibers. To interpret this in terms mainly of distal sprouting and expansion of the normal ipsilateral innervation may be premature. Subsequent work in rats indicates that chiasmal sprouting by fibers of the remaining eye may result in an extensive projection to the wrong (denervated) side of the brain (Cunningham & Freeman, 1974; Lund *et al.*, 1973). Until a similar possibility has been ruled out in the other relevant studies, it is somewhat idle to invest in possible explanations for any violation of chemoaffinity-determined connectivity.

An important possible exception to the foregoing is found in an anomalous ipsilateral collicular projection in the rat following unilateral enucleation, which appears to be a polar mediolateral inversion of that expected from chemoaffinity matching (Cunnigham & Speas, 1975). However, this finding is somewhat at odds with previous work indicating only a limited anomalous projection (Lund *et al.*, 1973; Lund & Lund, personal communication). Even if confirmed, some kind of chemoaffinity "flip-flop" or mechanical inversion of fiber growth path remains possible. In view of the indicated collicular pathology under these conditions and the presence of an appropriate organization along the rostrocaudal axis (Lund & Lund,

1971; Tsang, 1937), the conclusion that innervation is here determined independently of the tectum is hardly warranted (Cunningham & Speas, 1975).

Growth of optic fibers into centers where optic termination does not normally occur is almost entirely confined to areas that have been denervated or damaged simultaneously with extensive elimination of the normal terminal nuclei of the optic fibers, either by direct lesioning, as in the collicular experiments (Schneider, 1973), or by retrograde and possibly transneuronal effects, such as those produced in the lateral geniculate nucleus after striate cortex removal (Cunningham, 1972; Goodman & Horel, 1966). Under such conditions, with their normal terminal station removed, optic fibers are forced to seek alternative sites and may be supposed to invade first those that are pathologically attractive or stimulating as a consequence of the reaction to extensive denervation. It is an old observation that denervated tissue stimulates nerve fiber ingrowth and connections. The importance of denervation is indicated by observations on hamsters sustaining neonatal superior collicular lesions where, owing to variability in the lesioning technique, the inferior collicular projection to the medial geniculate body was differentially disrupted (Schneider, 1973). When this medial geniculate denervation was virtually complete, there was limited invasion by optic fibers. If only a small inferior collicular projection remained, however, little or no ingrowth was seen. This lack of invasion under the latter condition seems hardly attributable to an absence of synaptic space, but may be better accounted for by the absence of denervation pathology.

The evidence indicates generally that normal fibers are much better competitors for their appropriate termination sites than are foreign ones. Only a small fraction of normal fibers seems to be able to inhibit invasion by foreign fibers. Experiments in the septal nuclei of adult rats show this kind of inhibition of sprouting (Moore, Björkland, & Stenevi, 1971), and early studies on oculomotor reinnervation suggest that the original fibers can even displace foreign innervation after it is already established (Sperry & Arora, 1965; Marotte & Mark, 1970). The fact that optic neurons are physically capable of growing into the medial geniculate and other inappropriate but accessible areas but do not do so, even if some terminal space apparently remains available, argues for the operation in mammalian neurogenesis of selective chemoaffinity influences.

Further support for the notion that some of these novel connections in mammals are forced and are, in fact, second-order choices (not the preferred termination) comes from the above hamster studies of Schneider (1973), where, in addition to unilateral collicular lesioning, the optic innervation of the normal colliculus was eliminated by enucleation of the corresponding eye. Under these conditions the remaining optic fibers cross over to inner-

vate extensively the unlesioned denervated colliculus. Simultaneously the inappropriate terminations in the lateral posterior nucleus, found only after a collicular lesion, are reduced. Apparently an increase in the number of appropriate cells available for innervation acts to decrease termination in less appropriate areas.

More complete answers are hindered by serious gaps in our knowledge of even the normal, much less the altered, innervation of these systems. Whether different retinal ganglion cells project to different nuclei or whether the same cells send separate collaterals to the different areas is far from clear, and much less so the temporal sequence of the innervation process. The Fink–Heimer method, applied in normals, appears to show areas of variable projection (Lund *et al.*, 1973; Schneider, 1973), and one has to wonder whether the stain or other experimental factor may not be the variable. One of these "variable" areas is the lateral posterior nucleus of the hamster, a so-called "novel" projection area seen after collicular lesions. It is not entirely ruled out that this and perhaps even other "novel" projections might then be thought of as an amplification of a weak normal projection. Clearly, more evidence is needed before firm conclusions can be drawn.

Although the findings in lower vertebrates indicate a predominate lack of functional molding and modulation, the concept of chemoaffinity in synaptic patterning has never excluded additional effects of learning and other forms of functional plasticity. Observations on the effects of experience in shaping the visual system of mammals seem to indicate a significant functional influence in some species even in the primary visual cortex. The most dramatic examples have come from kitten-rearing experiments in which a surgically induced strabismus, or merely a few days of monocular deprivation during the fourth postnatal week, effectively disrupts the binocularity of cortical neurons (Hubel & Wiesel, 1970); or the exposure of otherwise dark-reared cats to a visual input consisting only of vertical or horizontal lines for even as little as 1 hour causes a pronounced corresponding bias in the orientation of cortical line-detecting cells (Blakemore & Cooper, 1970; Blakemore & Mitchell, 1973; Hirsch & Spinelli, 1970, 1971). Similar changes have been described following presentation for only a day of a moving vertical grating to an anesthetized paralyzed kitten deprived of prior visual experience (Pettigrew & Garey, 1974; see also Pettigrew, Olson, & Barlow, 1973).

Some of the accounts of these findings seem to take us back toward the position of more than 35 years ago, when it was believed that the animal builds its visual system mainly on the basis of environmental exposure and experience. Recent failures to confirm both the long-term (Maffei & Fiorentini, 1974) and short-term orientational effects (Stryker, 1974), plus disagreement on the extent to which line detectors develop without visual

experience (Hubel & Wiesel, 1963; Pettigrew, 1974), now complicate the picture.

In any case it appears that in mammals, as in lower forms, the great bulk of the visual system is patterned prefunctionally by the growth process itself. This applies even at the cortical level where a great wealth of structure, including the basic cytoarchitecture and retinotopic projection, binocularity, motion detection circuity, and some orientation selective cells and their basic functional relations can be shown to develop without visual experience. That line detectors of all orientation can be found even if kittens are reared seeing only vertical lines, provided this visual experience is not during the "critical period" (Blakemore, 1974), seems to argue against the fundamental wiring being determined by input. It has long been emphasized (Sperry, 1951a) that the role of function in preserving, reinforcing, or evoking what already is innately prepared and organized in development must be distinguished from that of adding new connections; but also underscored has been the increasing difficulty of keeping such distinctions meaningful as one progresses more deeply into the association centers of the brain (Sperry, 1965a). In general, environmental modification seems best conceived in terms of fine tuning or alignment processes, such as for stereopsis. This is suggested also in the apparent collective changes in receptive field position following small prism-induced disparities (Shlaer, 1971; see chapters in this volume by Grobstein & Chow and by Daniels & Pettigrew for full description).

Thus much of the literature on neural development in mammals directly supports the notion of chemospecificity. The various plasticities that stand out against this background of specificity of connections not only can be readily interpreted within the chemoaffinity framework, but on close examination much of the data would appear even to support it. At the same time these plasticities point up the role in neuronal development of function and of growth factors other than chemoaffinity.

IX. Conclusion

The literature on the formation of retinotectal connections, particularly in the last decade, appears to present numerous confusing discrepancies and contradictions that seem at first sight to defy any consistent interpretation. Further examination, however, along with some recent experimental findings, indicates that the great bulk of the available evidence can probably still be explained in terms of the original chemoaffinity theory only slightly modified by a few conceptual additions and refinements that emerge from the recent disparity and lesion studies.

Acknowledgments

Supported by the F. P. Hixon Fund of the California Institute of Technology and U.S. Public Health Service Grant No. MH-03372.

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